Journal of Surgical Oncology 1997;66:24–29

Patterns of Failure and Long-Term Results in High-Risk Resected Gastric Cancer Treated With Postoperative Radiotherapy With or Without Intraoperative Electron Boost

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Background: To evaluate the possible role of adjuvant radiotherapy in the management of high-risk resected gastric carcinoma.
Methods: From 1982 to 1993, 62 patients surgically resected of a primary gastric cancer with adverse pathological features (serosal and/or regional lymph node involvement) were treated with postoperative radiotherapy with (Group I) or without (Group II) intraoperative electron boost to the surgical bed and coeliac axis (IORT).
Results: After a median follow-up of 75.6 months (range 4–120+) for IORT patients and 91.2 months (range 6–149+) for non-IORT patients, overall relapse rates for Group I and Group II patients were 44.5% and 48.6% and local-regional relapse rates were 11.1% and 20%, respectively. Actuarial survival rates projected at the maximum follow-up were 41% and 38% in Groups I and II, respectively.
Conclusions: This retrospective analysis suggests a beneficial effect of adjuvant external radiotherapy in promoting local-regional control in high-risk resected gastric cancer.
J. Surg. Oncol. 1997;66:24–29.

KEY WORDS: **gastric cancer; adjuvant radiation therapy; intraoperative radiotherapy**

INTRODUCTION

Nodal involvement and/or serosal invasion represent major adverse pathological features in patients with primary resectable gastric cancer. In spite of ''curative resections,'' recurrence in locoregional sites represents the most common pattern of failure in patients with gastric cancer [1–3], with reported rates ranging from 40% to 90%, depending on tumor stage and type of failure analysis (clinical vs. reoperation or necropsy). Five-year survival rates after surgery have remained unchanged for decades, ranging from 10% to 40%, depending on the number of adverse prognostic features exhibited [2,4].

Radiation therapy has been used in the treatment of unresectable gastric cancer for palliation. In this group of patients, the addition of 5-fluorouracil (5-FU) to radiation therapy has demonstrated increased median survival promoting a small number of long-term survivors [5]. Subsequent trials have failed to confirm any advantage on the use of combined 5-FU and radiation therapy over 5-FU alone in this specific disease category [6].

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Accepted 6 May 1997

At the present time, the use of adjuvant treatments remains investigational. A recent meta-analysis on 11 adjuvant chemotherapy trials failed to show any statistically significant survival advantage in the treated groups (odds ratio 0.88) [7]. The use of radiation therapy as adjuvant treatment, combined or not with chemotherapy, has not proven to be superior over surgery alone. Only a small proportion of patients (ranging from 10% to 20%) with poor prognosis gastric cancer, including some patients with residual disease after surgery, may be cured with postoperative radiation therapy and 5-FU-based chemotherapy [8–11]. Initial data from the Gastrointestinal Tumor Study Group (GITSG) trial [9] showing better survival rates with chemoradiation have not been confirmed in subsequent randomized and nonrandomized trials [8,10–12]. Thus, at the present time, there is no evidence of benefit of any given treatment administered in the adjuvant setting over observation alone. However, several randomized studies [6,11,12] have all reported a decreased incidence of local-regional failure in patients treated with radiation therapy, when compared to chemotherapy or observation groups. This constant finding suggests a potential role for radiation therapy in the multidisciplinary management of high-risk resected gastric cancer, similar to what has been recognized in other gastrointestinal malignancies [13,14].

TABLE I. Gastric Cancer Patients: Tumor Characteristics Obtained From Surgical Specimens

Characteristics	Group I (%)[b]	Group II (%)[c]
Tumor location	(N = 27)	(N = 35)
Antrum	11 (40.7)	19 (55.8)
Corpus	3 (11.1)	11 (32.2)
Proximal	3 (11.1)	2 (5.8)
Linitis/multiple sites	7 (25.9)	1 (2.9)
Gastric remnant[a]	3 (11.1)	1 (2.9)
Tumor grade		
GI	3 (11.1)	2 (5.7)
GII	—	4 (11.4)
GIII	12 (44.4)	13 (37.1)
GIV	4 (14.8)	2 (5.7)
Unknown	8 (29.6)	14 (40.0)
Histologic type		
Diffuse	18 (66.6)	23 (65.7)
Intestinal	6 (22.2)	10 (28.6)
Mixed	1 (3.7)	—
Not specified	2 (7.4)	2 (5.7)
Modified Astler-Coller staging		
B2	8 (29.6)	6 (17.1)
B3	2 (7.4)	—
C1	3 (11.1)	8 (22.9)
C2	13 (48.1)	20 (57.1)
C3	1 (3.7)	1 (2.9)
Serosal invasion	24 (88.8)	27 (77.1)
Nodal involvement	17 (62.9)	29 (82.8)

[a]Previous subtotal gastrectomies due to peptic ulcer.
[b]Group I: patients treated with intraoperative radiation therapy.
[c]Group II: patients treated wtih postoperative radiation therapy alone.

TABLE II. Surgical Treatment Characteristics and Pathology Findings

Surgery	Group I	Group II
Type of procedure	(N = 27)	(N = 35)
Subtotal gastrectomy	5 (18.5)	14 (40.0)
Total gastrectomy	16 (59.2)	5 (14.2)
Extended gastrectomy	6 (22.2)	16 (45.7)
Pathology		
Nodal findings		
Nodes resected median (range)	13 (4–53)	15 (0–59)
Nodes involved median (range)	3 (0–29)	4 (0–23)
Resection margins		
Involved	4 (14.8)	2 (5.7)
Tumor free	23 (85.1)	33 (94.2)

The present analysis is a retrospective study of the patterns of disease progression and long-term results in 62 patients with high-risk (serosal invasion and/or regional nodes involvement) primary resected gastric cancer treated with postoperative radiotherapy with or without intraoperative electron boost to the surgical bed and nodal coeliac axis region, managed in a 10-year period. Our results with intraoperative radiotherapy, toxicity, and side effects have been reported previously [15]. This report is limited to those patients who have been treated by a combined modality approach at the time of the initial therapy, excluding patients with recurrent and/or unresectable disease.

MATERIALS AND METHODS

From October 1982 to March 1993, 62 patients with primary resected gastric cancer and confirmed adverse pathological features (serosal and/or regional lymph node involvement) were treated with postoperative radiotherapy. Twenty-seven patients additionally received an intraoperative electron boost (IORT) to the surgical bed and nodal coeliac axis region during the primary surgical procedure.

Patients have been divided for analysis into Group I with 27 patients treated with IORT plus postoperative radiotherapy and Group II with 35 patients treated with postoperative radiotherapy alone. Group I patients were treated during the time period 1985–1991, in which the IORT protocol remained active. Group II includes patients treated before the IORT program was available in our institution and after the date the IORT phase I–II trial was concluded. It also includes a small number of patients in whom IORT was not performed for different technical reasons.

Median age for Group I patients was 57.8 years (range 34–74) and 51.4 years for Group II patients (range 29–78). Patients have been staged according to the modified Astler-Coller Staging System [16]. Data regarding tumor characteristics are shown in Table I.

Surgical procedures included subtotal, total, and ex-

TABLE III. Gastric Cancer Study: Radiotherapy Technical Characteristics

	Group I	Group II
Postoperative radiotherapy	(N = 27)	(N = 35)
Dose, total (Gy) median (range)	46.0 (30–46)	45.0 (44–60)
Treatment time, elapsed days median (range)	32 (22–43)	35 (29–48)
Treatment area, sq cm[a] median (range)	239 (89–416)	244 (190–320)
Intraoperative radiotherapy (%)		
Dose (Gy)		
10	1 (3.7)	—
15	25 (92.6)	—
17	1 (3.7)	—
Beam energy (MeV)		
9	11 (40.7)	—
12	15 (55.6)	—
20	1 (3.7)	—
Cone size (cm ø)		
6–7	9 (33.3)	—
8–9	16 (59.2)	—
10	2 (7.4)	—

[a]After customized blocking.

tended radical gastrectomies according to the location of the tumor, regional spread, and surgeon's individual criterion and experience. In general, more extensive gastric and nodal resections were performed in the latter years of the study period. Relevant data regarding surgical treatment are shown in Table II.

Radiation portals were designed to encompass the surgical bed and the upper abdominal nodal regions as described by Gunderson and Sosin [1] using 15 MV photon beams (8 patients were treated with 45 MV betatron photons), anterior-posterior, posterior-anterior fields, all fields being treated every day with a 1.8–2.0 Gy standard daily fractionation delivering a total dose of 45–50 Gy. Custom made blocks were designed to spare as much kidney and liver tissue as possible. Five patients (one Group I, four Group II) received concomitant 5-FU-based chemotherapy. The complementary data regarding radiation therapy characteristics are described in Table III.

Local-regional failure was defined as failure in the upper abdominal space excluding the liver and including the tumor bed, anastomosis or stump, regional nodes and adjacent structures encompassed in the radiation volume. Peritoneal failure was defined as relapse in the peritoneal surfaces located outside the radiation volume. Distant failure was defined as recurrence in intrabdominal or extrabdominal organs other than those mentioned above. Mixed failure was defined as a combination of local-regional and/or peritoneal and/or distant relapse. Pathological verification of recurrent disease was not required for diagnosis of relapse, especially in those cases of obvious radiological evidence of distant metastases. However, an attempt was made histologically to verify all suspected cases of local-regional and peritoneal failure.

Results regarding patterns of failure are given in totals and rated values. Data regarding patient outcome are described as actuarial overall survival rates according to the Kaplan and Meier method and compared with use of the log-rank test [17]. Only those patients with a follow-up

TABLE IV. Patterns of Failure After Adjuvant Radiotherapy in Resected Gastric Carcinoma

Patterns of failure	Group I (%)	Group II (%)
	(N = 27)	(N = 35)
Local-regional, only[a]	1 (3.7)	2 (5.7)
Peritoneal, only	4 (14.8)	4 (11.4)
Distant, only	4 (14.8)	4 (11.4)
Mixed	3 (11.1)	7 (20.0)
Control	15 (55.5)	18 (51.4)
Local-regional, any[b]	3 (11.1)	7 (20.0)
Peritoneal, any	7 (25.9)	10 (28.5)
Distant, any	5 (18.5)	10 (28.5)
Relapse sites	Group I	Group II
Local-regional		
gastric bed	2	4
anastomosis	1	2
coeliac nodes	—	1
Distant		
lung and pleura	3	5
liver	1	4
supraclavicular nodes	1	—
bone	2	2
abdominal wall	1	—
ovary	—	1
retroperitoneal nodes	—	1
brain	—	1
periadrenal tissue	—	1
pericardium	—	1

[a]Individual patterns of failure observed.
[b]Total patterns of failure observed (mixed failures have been incorporated into individual patterns of failure).
[c]More than one site per patient.

TABLE V. Patterns of Failure by Stage After Adjuvant Radiotherapy in Resected Gastric Carcinoma

	Group I (N = 27)					Group II (N = 35)			
	B2	B3	C1	C2	C3	B2	C1	C2	C3
Local-regional, only[a]	—	—	—	1	—	1	—	1	—
Peritoneal, only	—	1	—	3	—	1	—	3	—
Distant, only	—	1	1	2	—	—	1	3	—
Mixed	—	—	—	2	1	—	2	4	1
Number failed/total	0/8	2/2	1/3	8/13	1/1	2/6	3/8	11/20	1/1
Local-regional, any[b]	—	—	—	3	—	1	2	3	1
Peritoneal, any	—	1	—	5	1	1	1	7	1
Distant, any	—	1	1	2	1	—	3	7	—

[a]Individual patterns of failure observed.
[b]Total patterns of failure observed (mixed failures have been incorporated into individual patterns of failure).

of at least 18 months were considered eligible for analysis of patterns of failure and survival.

RESULTS

Overall relapse rates for Group I and II have been 44.5% and 48.6%, respectively (Table IV). Peritoneal and distant recurrence were the most frequent types of progression in both treatment groups. Isolated local-regional failure was an uncommon finding, usually seen in combination with other out-of-the-radiation-field documented sites of disease progression. Local-regional failure was more frequent in Group II than in Group I patients (20.0% vs. 11.1%), although this difference is not statistically significant ($P < 0.38$). Local-regional, peritoneal and distant relapses were histologically verified in 80%, 58.8%, and 26.6% of the cases, respectively.

Analysis by stage, as expected, showed a higher relapse rate in C2 patients when compared to the B2 subset, in both treatment groups. Local-regional failures were only observed in the C2 subset among Group I patients, whereas this feature appeared in all disease stages in Group II patients (Table V).

After a median follow-up of 75.6 months (range 4–120+) for Group I patients and 91.2 months (6–149+) for Group II patients, actuarial overall survival rates projected at the maximum follow-up, are 41% and 38%, respectively. Survival curves are shown in Figures 1 and 2 and patient outcome is described in Table VI. It is important to note that four patients in Group I had treatment-related deaths, three of them died of gastrointestinal bleeding probably associated with IORT and one of enteritis. One patient in each group died of non treatment-related causes (cardiovascular and traffic accident).

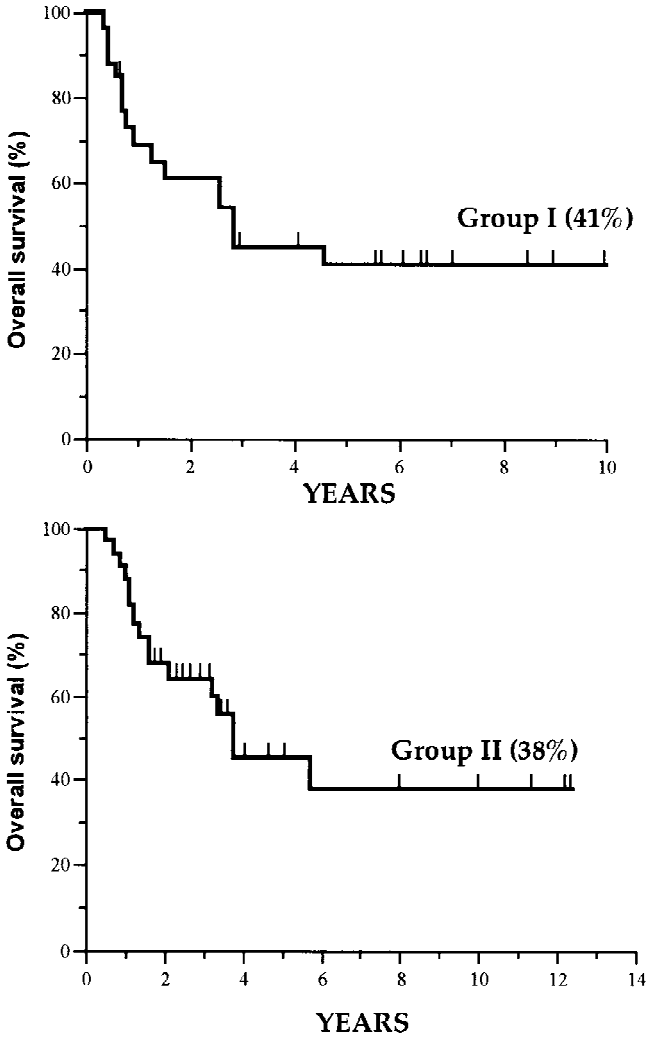

Fig. 1. Overall survival rates for Groups I and II.

DISCUSSION

Local-regional control continues to be a crucial goal of therapy for gastric cancer. Classic articles focusing on this issue have demonstrated very high rates of failure in local-regional sites after ''curative resections.'' In this respect, Gunderson and Sosin [3] analyzed the patterns of failure in a series of 107 patients with programmed reoperations 6–18 months after initial surgery (68 patients) or, when evidence of recurrence or metastatic disease (39 patients), reporting a component of local-regional failure in 87.8% of the relapsing patients. The disease categories of the patients included in their analysis are quite similar

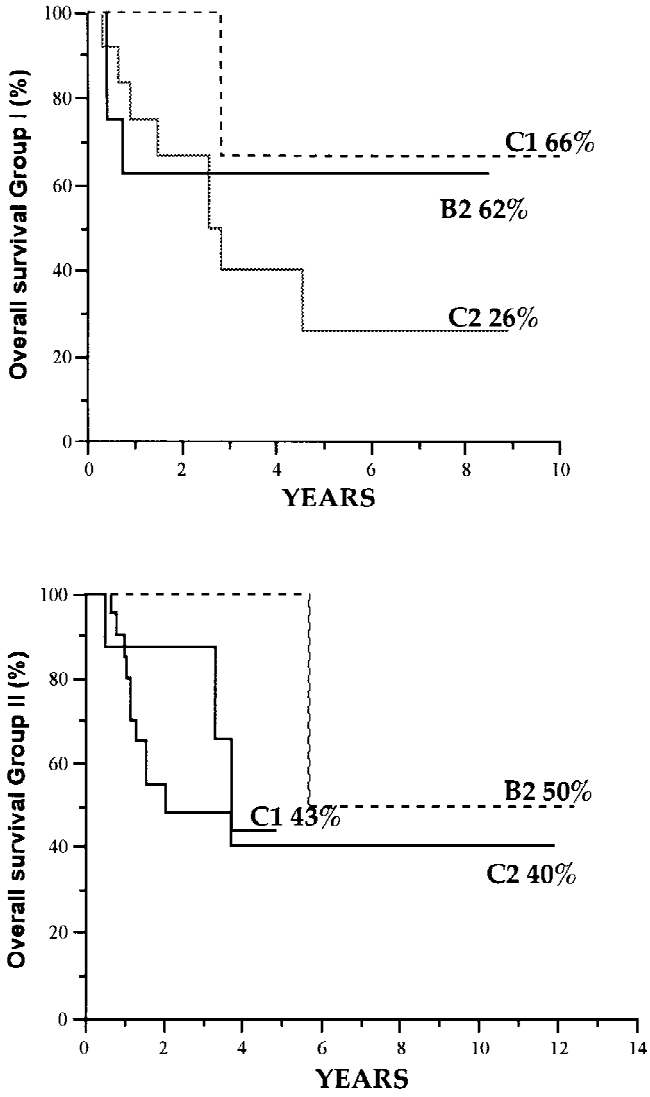

Fig. 2. Overall survival rates according to the Modified Astler-Coller staging for both Groups I and II.

to the present experience, although they had a small proportion of patients with early-stage gastric cancer. The figures for local-regional relapse are even higher in the article reported by Wisbeck and co-workers [3]. These authors, in a series of 16 necropsies performed in patients formerly operated for resectable gastric cancer, reported the occurrence of recurrent disease in local-regional sites in 15 of them (94%). Both reports indicate that local-regional failure is an almost universal and early event in the natural history of resected gastric cancer. Reoperation and necropsy information is extremely useful in our understanding of actual patterns of failure in gastric cancer; however, most gastric cancer trials provide patterns of failure data based on clinical grounds alone. It is not surprising that when patterns of failure are evaluated mainly by clinical observation, the actual failure rates may well be underestimated. In this respect, Landry and co-workers [2], evaluating the patterns of failure of 130 patients treated with curative resection at Massachusetts General Hospital, reported a component of local-regional failure in 38% of the patients. The suspected local-regional recurrence were histologically verified in 69% of the cases. The local-regional failure rate observed in the present analysis (11% Group I, 20% Group II) after an overall median follow-up longer than 7 years is striking when compared to that of previous experiences, including recent IORT phase II trials [18]. Although it could be argued that clinical observation, with histological verification, is not the most reliable method to estimate the incidence of local-regional failure for resected gastric cancer, it should be noted that >50% of the patients in the present series did not show clinical evidence of recurrent disease after a prolonged follow-up, suggesting a beneficial effect of adjuvant radiotherapy in the promotion of local control for resected gastric cancer. The results in terms of local-regional control for the patients treated with IORT are not significantly superior, but no definitive conclusions can be drawn due to the occurrence of several early toxic deaths in the IORT group—described in part in a previous report [19]—and the retrospective, nonrandomized nature of this analysis.

TABLE VI. Patient Outcome in Current Study

Outcome	Group I (%)	Group II (%)
	(N = 27)	(N = 35)
Alive and well	10 (37)	17 (49)
Dead with disease	11 (41)	16 (46)
Alive with disease	1 (4)	1 (3)
Dead free of disease	5 (19)	1 (3)

An improved local-regional control in those patients receiving adjuvant radiotherapy also has been reported by different authors. Moertel et al. [11], in a series of 62 patients with poor prognosis gastric cancer randomized to observation or combined 5-FU and radiotherapy (3,750 cGy ± 200 cGy), reported an incidence of local-regional failure in 39% of the patients in the treatment arm vs. 54% in the observation group. Allum [12], in a series with 436 patients randomized to observation, adjuvant radiotherapy (45–50 Gy) or FAM (Fluorouracil, Adriamycin, Mitomycin C) chemotherapy, reported a local-regional failure rate of 27% for the control group, 19% for the chemotherapy arm, and 10% for the adjuvant radiation arm ($P < 0.01$). Unfortunately, two GITSG randomized studies comparing postoperative chemotherapy vs. chemoradiotherapy [9,10] do not provide data regarding patterns of failure. These results suggest that 45–50 Gy administered postoperatively are effective in controlling subclinical disease in a large number of patients free of visible tumor after surgery who would otherwise relapse in local-regional sites.

The role of IORT in gastric cancer is still investiga-

tional. Improvement in local control is the rule in selected studies using IORT [15,20], without any survival advantage in the randomized trials published to date [20,21]. The results obtained from the current study favors the trend of increasing local control with postoperative radiotherapy and a small but even better locoregional disease control in the IORT-treated patients.

CONCLUSION

Locally advanced gastric cancer, including stages B2 to C3, has demonstrated poor overall survival rates, ranging from 37% to 9%, respectively [2]. Surgical results have not been improved by adjuvant therapy in several decades [6,7,10–12]. The present report indicates a mature survival plateau near the 40% limit and a local control rate >80%, which suggest, but do not prove, a possible favorable effect of adjuvant radiotherapy. IORT, as a component of adjuvant radiation therapy treatment, promotes better local control rates, but its possible value is diluted in this particular experience by the occurrence of several lethal complications in a clinical experience limited to a small number of patients. These results should be confirmed in a randomized trial.

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